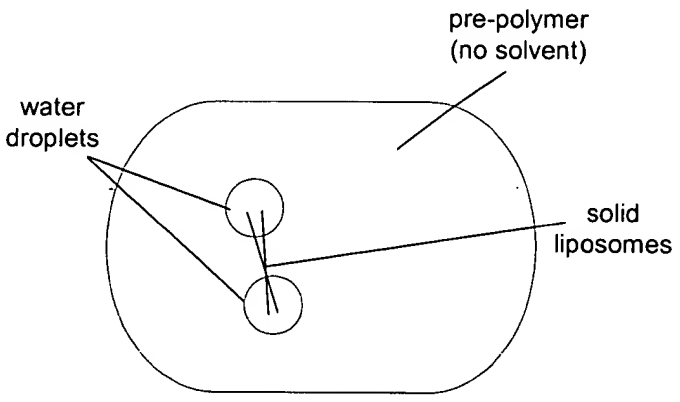
Applicants respond that the '481 reference does not teach or suggest their claimed invention. The disclosure on page 12, line 29 and page 13, line 9 is the passage cited by the Examiner as support for the assertion of an emulsion of an aqueous carrier in polymer. The pertinent part of that passage recites as follows:

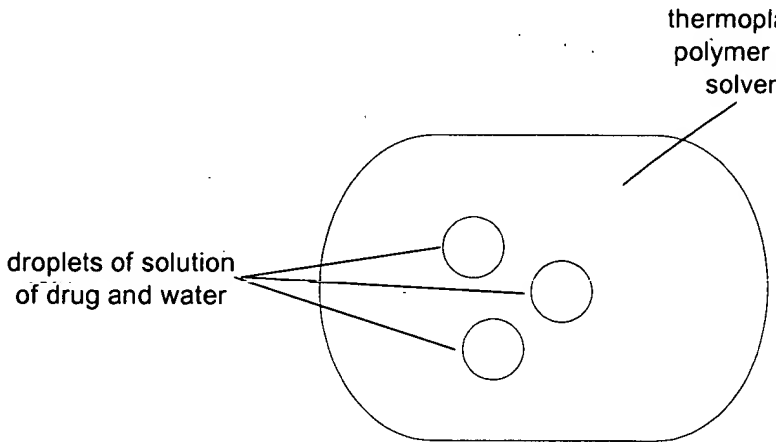
> Liposomes containing the active agent typically are formed in an aqueous solution by one of a [sic] well-known methods (see e.g. U.S. Patent 5,049,386). The aqueous solution containing the liposomes may be incorporated in the compositions of the present invention, for example by forming a water-in-oil emulsion of this solution in a liquid pre-polymer. After curing, a polymer matrix with the liposomes embedded therein is formed.

The liposomes described in this passage are made according to the method described in U.S. Patent No. 5,049,386 (copy enclosed). According to the '386 patent, Example 4, the liposome forming material and drug are dissolved in an organic solvent such as chloroform, and the solvent removed to provide a film of a mixture of the drug and liposome forming material. The film is suspended in aqueous solution (indicating it is insoluble in the aqueous solution) and sonicated to clarity. The sonication shatters the film to form microparticles of film suspended in the aqueous solution.

Thus, the aqueous solution added to the liquid pre-polymer according to the '481 reference consists of solid microparticles of a drug-liposome mixture suspended in water. When this suspension is incorporated into the prepolymer to form an emulsion, the water droplets do not contain dissolved drug. Instead, they contain solid particles of the liposome-drug mixture. This arrangement can be pictured as follows:



In contrast, the emulsion according to the present invention has the drug dissolved in the water droplets. No solid agent isolating the drug from the water droplets is present. This arrangement can be pictured as follows:



Additional differences also exist. The liquid pre-polymer described by the '481 reference is not a thermoplastic polymer. As the '481 reference indicates at page 23, line 36 through page 25, line 4, the liquid pre-polymer is the precursor of a thermoset polymer. It is a liquid by itself. It is not a solid polymer that requires a solvent to form a liquid. Thus, the phrase "liquid pre-polymer is a phrase describing pure pre-polymer, i.e., it is neet pre-polymer. Consequently, the '481 reference discloses addition of the liposomes in water to the neet thermoset prepolymer. No solvent is present. In contrast, Applicants claim a system containing organic solvent and thermoplastic polymer. That polymer is a solid, not a liquid in its neet state. Moreover, it does not cure to a cross-linked thermoset polymer as is true of the pre-polymer of the '481 reference.

One might retort that the quoted passage is not limited to the pre-polymers. The passage discloses that "the liposomes may be incorporated into the compositions of the present invention". Those compositions include the thermoplastic polymers as well as the thermoset polymers. Thermoplastic polymers are the polymers recited in Applicants' currently pending claims.

However, the '481 reference, in fact, leads away from the present invention. The '481 reference discloses at page 5, lines 10-33 and at page 18, line 33 - page 19, line 25 that when a solution of a water-insoluble, thermoplastic polymer in organic solvent contacts an aqueous

medium, the polymer coagulates to form a solid. Thus, according to the '481 reference, if a thermoplastic polymer in organic solvent were mixed with an aqueous medium containing liposomes as described at page 13 of the '481 reference, the thermoplastic polymer would solidify.

Applicants have discovered, in contrast to this '481 disclosure, that if a low water solubility solvent is combined with the thermoplastic polymer, an emulsion with water can be formed without causing solidification of the polymer. Applicants teach this phenomenon in Example 1 and contrast it with the teaching of Example 2 of their application. Indeed, Example 2 confirms the disclosure of the '481 reference that under certain circumstances, attempting to form an emulsion of water and a solution of thermoplastic polymer in organic solvent results in solidification of the polymer. Those circumstances involve use of highly water soluble organic solvents.

For these reasons, Applicants submit that their claimed invention is patentable over the disclosure of the '481 reference. Applicants respectfully request withdrawal of this rejection.

The Examiner has also rejected the pending claims under 35 USC § 102(e) as being anticipated by Brodbeck et al. (U.S. Patent No. 6,130,200). The Examiner asserts the Brodbeck discloses a gel containing a polymer a solvent of less than 20% water solubility, an active agent and an emulsifying agent. The emulsifying agent may be water.

Applicants respond that their claims as amended are patentable over Brodbeck. Applicants claim a delivery system in which the bioactive agent (drug) is contained within the aqueous droplets of the non-continuous phase of their emulsion. The continuous phase of Applicants' system contains the polymer and an organic solvent having from about 2% to about 20% water solubility. In contrast, Brodbeck discloses a delivery system of emulsified gel of organic solvent and polymer in which the drug is dissolved within the gel. Brodbeck does not put his drug in his emulsifier when he uses solvents having some water solubility. Only when Brodbeck uses an alkyl or aralkyl benzoate as the organic solvent, does he put his drug in his emulsifier. However, these solvents have **no** water solubility according to the "Handbook of Chemistry and Physics" 42nd ed. (copy of relevant pages for methyl benzoate and benzyl benzoate enclosed.) Consequently, Brodbeck leads away from Applicants' invention. Brodbeck

discloses that the drug can be placed in his emulsifier only when a solvent having **no** water solubility is used.

In the following discussion, Applicants explain the details of this argument.

Brodbeck discloses in his "Summary of the Invention" a number of aspects of his invention. His first statement (col. 4, line 66-col. 5, line 2) is that his system comprises "a beneficial agent dispersed or dissolved substantially throughout a viscous gel". He explains several variations of this system (col. 5, lines 8-55) wherein each variation has the beneficial agent dissolved or dispersed in the viscous gel composition. (See for example the description at col. 5, lines 38-40). He explains that for each variation, the viscous gel is a combination of a biocompatible polymer and a solvent having less than 7% water solubility.

At col. 5, line 58-col. 6, line 24, Brodbeck describes further details of this gel composition. It contains the polymer, the solvent, the beneficial agent and optionally an emulsifying agent. According to Brodbeck's descriptions, the beneficial agent or drug is dissolved or dispersed throughout the gel. This, Brodbeck teaches placement of the drug into the polymer-solvent solution rather than into the water emulsifier as Applicants do.

Brodbeck then carefully describes two of his preferred gel compositions. Both are limited to alkyl and aralkyl esters of benzoic acid as the organic solvent. In the first of these two, Brodbeck explains that the beneficial agent is mixed with the emulsifying agent (col. 6, lines 45-61). In the second of these two, Brodbeck explains that the beneficial agent is dispersed or dissolved in the viscous gel (col. 6, line 62 - col. 7, line 7). Brodbeck carefully describes these benzoic acid ester compositions and treats them differently compared with his other compositions.

Brodbeck certifies this differentiating treatment by providing his overall description of the invention in the first few paragraphs of his "Detailed Description of the Invention". He states that his "implantable system is formed as a viscous gel from a biocompatible polymer and biocompatible solvent, and a beneficial agent substantially dissolved or dispersed throughout the gel"(col. 8, lines 38-40). He continues with his explanation of this system by describing it as often being highly viscous. To lower the viscosity and enable injection, Brodbeck discloses that he adds an emulsifier (col. 9, lines 9-12). Thus, the purpose of the emulsifier according to

Brodbeck is to lower viscosity. Brodbeck does not use the emulsifier to protect the agent or generally dissolve it as Applicants do.

Upon reading Brodbeck's disclosure, one of skill would conclude that only when the organic solvent is completely insoluble in water can one mix drug with an emulsifying agent that is water. In all other situations, the drug is to be mixed with the viscous gel according to Brodbeck.

Therefore, Brodbeck leads away from a formulation of a drug - water mixture which is emulsified with a solution of thermoplastic polymer and a low water soluble solvent. Brodbeck would put the drug in the polymer - solvent solution and not in the water. Applicants' claimed invention is that contraindicated formulation: an emulsion of a drug- water mixture in a solution of polymer and low water soluble solvent. Consequently, Brodbeck does not anticipate or suggest Applicants' claimed invention.

For these reasons, Applicants submit that their claimed invention is patentable over Brodbeck. Applicants respectfully request withdrawal of this rejection.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to telephone Applicant's attorney (612-373-6939) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date 12-28-01 By _____
Leif T. Stordal
Reg. No. 46,251

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 28th day of December, 2001.

Dawn M. Poole
Name

Dawn M. Poole
Signature

Docket No. 01195.157US1
WD # 416533.wpd

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OIPE JC88

Clean Version of Pending Claims

EMULSIONS FOR IN-SITU DELIVERY SYSTEM
Applicant: Richard L. Dunn
Serial No.: 09/060,047

1. (Amended) A composition for delivering a biologically active agent, comprising: an emulsion of a biologically active mixture and a controlled release formulation, the biologically active mixture comprising the biologically active agent and a pharmaceutically acceptable, aqueous medium as a protective carrier; and the controlled release formulation comprising a pharmaceutically acceptable, biodegradable thermoplastic polymer that is substantially insoluble in an aqueous or body fluid and a pharmaceutically acceptable organic solvent having a water solubility of from about 2 percent to about about 20 percent by weight relative to a weight of a combination of organic solvent and water.

2. A precomposition suitable for preparing a composition according to claim 1, comprising separate containers of the biologically active mixture and controlled release formulation, which containers are adapted to cause combination of the biologically active mixture and controlled release formulation.

3. A composition of claim 1, wherein the biologically active agent is selected from the group consisting of an antiinflammatory agent, an antibacterial agent, an antifungal agent, an analgesic agent, an anesthetic agent, an immunogen, a vaccine, an antineoplastic agent, a growth or survival agent, a hormone, a cardiovascular agent, an anti-ulcer agent, a bronchial agent, a central nervous system agent, a gene, a gene fragment, an insertion vector carrying a gene or gene fragment, and any combination or multiple thereof.

14. (Amended) A composition of claim 1 wherein the thermoplastic polymer formula contains monomeric units selected from the group consisting of lactide, glycolide, caprolactone, anhydride, amide, urethane, esteramide, orthoester, dioxanone, acetal, ketal carbonate, phosphazene, hydroxybutyrate, hydroxyvalerate, alkylene oxalate, alkylene succinate, amino acid and any copolymer and terpolymer combination of these monomeric units in random order or in block order.

C3

15. A composition of claim 14 wherein the monomeric units include lactide, glycolide, caprolactone, hydroxybutyrate, and any combination thereof.

19. A composition of claim 1, wherein the emulsion is a water-in-oil emulsion.

28. A composition of claim 1 wherein the thermoplastic polymer is in mixture with a non-polymeric material.

29. A composition of claim 1 wherein the aqueous carrier is water, saline, physiological buffer solution, cell-culture medium, aqueous nutrient medium, aqueous mineral medium, aqueous amino acid medium, aqueous lipid medium, aqueous vitamin medium or any combination thereof.

30. (New) A composition of claim 1 wherein the organic solvent is selected from the group consisting of esters of carbonic acid and alkyl alcohols, alkyl esters of mono-, di- and tricarboxylic acids, and alkyl ketones.

31. (New) A composition of claim 1 wherein the organic solvent is selected from the group consisting of propylene carbonate, diethyl malonate , ethylene carbonate, dimethyl carbonate, 2-ethoxy ethyl acetate, ethyl acetate, methyl acetate, ethyl butyrate, diethyl glutonate, tributyl citrate, diethyl succinate, tributyrin, isopropyl myristate, dimethyl adipate, dimethyl succinate, dimethyl oxalate, dimethyl citrate, triethyl citrate, acetyl tributyl citrate, glyceryl triacetate, methyl ethyl ketone, tetrahydrofuran,